The concept of ventricular/vascular coupling: functional and structural alterations of the heart and arterial vessels go in parallel

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The concept of coupling

The arterial circulation and left ventricle (LV) are two functional units who are joined together to form a coupled biological system. The interaction between the heart and the arterial system is designed to maximize delivery of power generated by the heart to the circulation. Optimal coupling depends on: (i) the intrinsic properties of the LV and (ii) the physical properties of arterial system. Acute changes in LV or vascular functions activate neurohumoral mechanisms. Matching of cardiac and arterial functions is then achieved, among others, by alterations of heart rate, of myocardial contractility, and of vascular tone. As such acute compensations tend to increase metabolic demand, optimal mutual adaptation of cardiac and vascular function in chronic conditions is completed by structural changes to normalize expenditure of energy. To optimize cardiovascular function in situations of chronic changes in cardiac and/or vascular function, remodelling of the heart and arterial vessels occurs in parallel as demonstrated by the findings in essential hypertension and end-stage renal failure [1,2].

The initiating signals for remodelling

Cardiac and vascular remodelling is triggered by sustained haemodynamic overload and modulated by additional non-haemodynamic and genetic factors. The increased haemodynamic burden may result from pressure and/or volume overload. The primary mechanical signal in pressure overload is tensile stress, while volume overload results in changes of shear rate and shear stress. Cardiovascular remodelling is aimed at maintaining such stress within the normal range [3].

According to Laplace’s law tensile stress (σ) is directly proportional to arterial and/or ventricular pressure (P) and radius (r), and inversely proportional to arterial and/or ventricular wall thickness (h). This follows from the well known formula: $\sigma = \frac{Pr}{h}$. In response to an increase in pressure or radius, tensile stress can be maintained constant when the ventricular and/or arterial walls thicken.

In laminar flow conditions (as occurs normally in arteries) shear stress (τ) is directly proportional to blood flow (Q) and blood viscosity (μ) and inversely proportional to the radius (r) of the vessel. This follows from the well known formula: $\tau = \frac{4Q\mu}{pr^3}$. An increase in shear stress can be the consequence of increased blood viscosity, decreased arterial diameter, or increased blood flow acting on endothelial surface. The characteristics of cardiovascular remodelling depend in large part on the nature of the initiating haemodynamic stimuli.

The responses of cardiovascular structures

The primary response to pressure load are (i) hypertrophy of the arterial and/or ventricular wall and, (ii) decrease of the ratio of the width of the lumen to the width of the wall. The classical example of pressure-mediated remodelling is the parallel increase in arterial wall thickness and concentric hypertrophy of the left ventricle in essential hypertension [1,4–6]. The classical example of flow-mediated remodelling are the changes in the radius of the LV and the vessels in hypervolaemia, anaemia or A-V fistula [3,7–10]. Excentric hypertrophy of the LV, and arterial dilation observed after creation of arteriovenous fistula is the paradigm of volume-overload mediated remodelling [2,9,10]. Distension of the LV with an increase in LV radius causes an increase in wall tension which is compensated by proportional wall hypertrophy [3]. In the arteries, the increase in radius normalizes shear stress.
Nevertheless, the increase in arterial radius increases tensile stress which must be compensated by a proportional increase in wall thickness (Figure 1).

The cardiac and vascular coupling in end-stage renal disease

As the changes in shear and tensile stress are interrelated (Figure 1), it is frequently difficult in cross-sectional clinical studies to assess whether arterial and/or ventricular remodelling result from primary increase in pressure or from primary volume/flow overload. The dilemma is well illustrated by the situation in ESRD. Studies with ESRD patients showed a direct relationship between the dimensions of major arteries and of the LV [2]. Conditions such as anaemia, arteriovenous shunts and overhydration induce a state of chronic volume/flow overload. This in turn is associated with an increase in the internal dimensions of the left ventricle and development of ventricular hypertrophy [11]. The chronic increase in cardiac output and arterial flow, however sets the stage for enlargement of arterial lumen [2,9]. Thus, the parallel action of flow overload on the arteries and on the left ventricle causes coupling between the heart and the conduit vessels as far as changes in their dimensions are concerned. The increase in arterial and ventricular radius is responsible for augmentation of tensile stress that induces a compensatory increase in intima-media thickness and in LV mass. In patients with ESRD the hypertrophy of the arterial wall hypertrophy is accompanied by alterations in vascular architecture [12] and by an increase in arterial stiffness. These changes contribute to amplify the effects of pressure load on LV hypertrophy [2], since an increase in circumferential tensile stress is often present as a result of increased arterial pressure [3–5]. Figure 2 shows the interrelations between the flow and pressure related factors on ‘coupled’ cardiac and vascular alterations and the postulated modulatory influence of the uraemic milieu on left ventricular as well as arterial functions (Figure 3).

The mechanotransduction

The processes of force transmission from the blood to the cells and force transduction within the cells are in general poorly understood. The process of transforming changes of mechanical forces into remodelling of cardiovascular structures implies that there are ‘sensors’ that detect and transmit physical forces to effector cells. This will be followed by synthesis and release of growth factors and vasoactive substances with paracrine/autocrine action that change cell growth, cell division and the balance between synthesis and breakdown of extracellular matrix [13,14]. While the endothelial cells are strategically situated at the blood-cardiovascular walls interface, and thus are a principal candidates for the role as sensors, other cells may also participate in providing signals for remodelling. The endothelial cell is principally involved in transduction of shear stress which causes changes in the shape and orientation of endothelial cells, and integrins mediated cytoskeletal alterations. These changes result in activation of mechanosensitive ions channels and activation of second messenger systems [13–21]. Substances released by endothelium influence the growth, proliferation and migration of vascular smooth muscle cells. However, it is likely that vascular smooth muscle cells, in addition, respond directly to increase in stretch and tensile stress changing their phenotype from contractile to secretory [13,14].

Similar messengers causing parallel structural modifications of heart and arterial vessels?

While the remodelling of the LV and arteries is initiated by similar mechanical forces, it remains uncertain whether the messenger systems and factors involved in these changes are the same in the heart and the vessels. Several hormonal and growth factors are capable of stimulating growth and proliferation in the candidate cells involved, i.e. smooth muscle cells, endothelial
cells, fibroblasts and cardiomyocytes. In patients with ESRD Demuth et al. [22] documented a significant correlation between increased plasma endothelin (ET) and increase in LV mass and in common carotid artery wall thickness. Myocardial and vascular ET expression is induced by pressure and volume overload. Furthermore, ET is a mitogen, stimulating growth and proliferation in a variety of cells such as smooth muscle cells, endothelial cells, fibroblasts and cardiomyocytes [23–26]. Thus, haemodynamic abnormalities observed in ESRD patients could alter release of ET which may in turn modulate the structure and function of the cardiovascular system. Nevertheless, ET is predominantly an autocrine/paracrine factor and a trophic role of circulating ET remains uncertain. Furthermore the study by Demuth et al. [22] is cross-sectional and correlative and does not demonstrate whether the increased plasma ET levels are the cause or the consequence of cardiovascular alterations observed in ESRD patients. Although the ET could be an ‘effector’ of mechanotransduction and cardiovascular remodeling only studies using ET receptors antagonists could clarify the pathogenic role of ET in cardiovascular pathology in ESRD patients.

References


